CALABAR BEAN.

The following account is for the most part an abstract of Dr. Fraser's very valuable and elaborate investigations concerning the physiological action of the calabar bean.

He finds that this poison destroys birds most easily, while frogs require as much as will kill a dog.

Little is known at present of the influence of the Calabar bean or its alkaloid on the structure of the stomach. Dr. Fraser has ascertained that gastric juice does not destroy the power of this drug; and further, when solutions of it are injected into a vein, they may be detected in the contents of the stomach, whence it has been concluded that the active principle is eliminated by this organ. It is, however, possible for it to find its way here by mere imbibition.

The active principles of Calabar bean quickly enter the blood. After small but fatal doses, the animal at first, and very speedily, manifests a slight tremulousness, which, beginning in the hind-quarters, spreads thence to the rest of the body. Soon the posterior limbs grow powerless, next the anterior extremities, and then the trunk, till muscular movement ceases, and the whole animal frame becomes limp and flaccid. There is general paralysis. The bowels and bladder are emptied involuntarily, and the pupils generally contract. At this stage all reflex action of the cord is destroyed; for if the animal is anywhere irritated, no contractions respond to the call. Under the influence of the poison, respiration grows gradually slower and slower, and at last ceases. So long as the animal retains the power of expression, evidence of consciousness appears to be preserved throughout. Immediately after death the pupils dilate. After death the muscles appear to be unaffected; for they contract as they are cut, and respond to irritation of their nerves. The heart, moreover, continues to beat the usual time after death, its parts ceasing to contract in their definite order. After a large fatal dose, the symptoms and *post-mortem* appearances

are much the same as those just described, but of course death occurs sooner, and the symptoms follow each other in quicker succession. After a very large dose, death may be almost instantaneous. It appears to be owing to syncope; for when the body is open, the heart is found motionless, dilated, flaccid, and contracts but languidly on stimulation. The vermicular movements of the intestines are also more sluggish than after a smaller dose.

Whether Calabar bean produces its effects by influencing the muscles, nerves, cord, or the brain, are questions which will now be severally considered.

As muscular contraction could be easily and abundantly excited by direct irritation of the muscles, after the motor nerves had quite lost their power to conduct impressions, Dr. Fraser concludes that this poison exerts no influence on the voluntary muscles. Moreover, the contractility continued a long time after death, and in frogs the rigor mortis was long postponed, while it certainly was not hastened in warm-blooded animals,—additional evidences of the absence of any paralyzing influence on the muscles by Calabar bean. The tremors in warm-blooded animals were generally slight, but were sometimes excessive, and might indeed be called convulsions, and were due probably to the direct action of the poison on the muscles, like curare; for if the sciatic nerve was divided before poisoning the animals, the limb thus cut off from nervous connection with the nervous centres still trembled; while, on the other hand, if the sciatic nerve was uninjured, but the arteries leading to the limb were tied or divided, then, while the muscles of the body generally trembled, those of the ligatured limb remained at rest. This tremulousness often continues after death, and is excited by exposure and by the knife in cutting. It does not affect the whole muscle at the same time, but different parts in succession.

Observing that consciousness is intact when paralysis is marked and progressing, and that if a frog's brain is removed before the animal is poisoned, paralysis ensues as

usual, Dr. Fraser concludes that the paralysis is not produced by any changes in the brain; but from the effects of the drug on himself he thinks the bean does exercise some influence on the faculties of the mind.

That paralysis is not produced by the action of the poison on the spinal nerves is evident; for long after the induction of general paralysis, and even after death, they conduct motor impressions to the muscles.

But though muscular paralysis and death are not to be accounted for by the action of the poison on the motor nerves, but in another way, as we shall shortly see, still after a time the poison does affect these nerves, and robs them of their power to conduct impressions to the muscles. As with conium, so probably with Calabar bean, the peripheral terminations of the nerves are first affected, and next their trunks: The afferent nerves remain unaffected, and certainly their power of conduction is not lessened; indeed, Fraser thinks it is increased.

The spinal cord, then, is the only part left on which the paralysis can depend, and Fraser has shown that the paralysis of the muscles is due to changes effected by Calabar bean on the cord. Thus he found he could excite no muscular contractions by galvanizing any part of the cord of an animal poisoned by the bean, while the motor nerves still retained their functions, and easily transmitted impressions to the muscles, which on their part freely responded to very slight stimulation of their proper nerves.

The reflex functions of the cord were destroyed long before the nerves lost their conducting power. For after the loss of reflex power in animals poisoned by Calabar bean, pretty active muscular contractions could be excited by mild galvanic stimulation of the motor nerves, showing that the arrest in reflex action is not owing to lowered activity of the motor nerves. Again, if the lower half of the cord is protected from the poisoned blood by ligature or section of its vessels, while the blood is permitted to flow to all other parts of the body, and the animal is then poisoned, reflex action

is speedily lost in the anterior, while it is retained for hours in the posterior limbs. As the nerves of every part of the body are equally subjected to the poison, the loss of reflex power cannot be due to alterations in them, otherwise the hind and front limbs would be equally paralyzed. The only part protected from the poison was the lower half of the cord, and it must be that Calabar bean destroys reflex power through the changes produced in the cord itself.

From its physiological action on the cord, Fraser recommends the ordeal bean as an antidote to strychnia, and he points out its superiority to curare, which paralyzes only the motor nerves, while the Calabar bean paralyzes first the cord, and then, after some time, the motor nerve.

Large doses of the bean instantaneously arrest the movements of the heart; smaller doses reduce their frequency.

Fraser contrasts Calabar bean with other cardiac poisons, such as antiaris toxicaria, tanghinia venenifera, digitalis, helleborus niger, helleborus viridis, and the green resin of nereum oleander, all of which, after a time, diminish the frequency of the heart's contractions by prolonging the systole, and finally stop the heart in the systolic act. Physostigma also diminishes the number of the heart's contractions, but it lessens the duration of each systole, and at last the heart ceases to beat in the diastole.

How does Calabar bean effect these changes in the functions of the heart? The paralysis of the heart in diastole, and the diminution in the frequency of its contractions by protracted periods of rest in a *dilated condition*, as well as the frequent renewal of its action after a long pause in diastole, might, in the first place, suggest the interference of the inhibitory functions of the vagi nerves. Fraser, however, adduces conclusive experiments against this supposition. Thus, he finds, after section of each vagi, or after paralyzing them with curare, (which it effects in a few minutes in both the motor and vagi nerves,) Calabar bean acted on the heart just as before. Again, when, previous to their being poisoned, the brain and cord of frogs were destroyed, the bean produced the same effects on the heart.

Physostigma is no doubt a respiratory poison, and in many instances destroys life by asphyxia; but Fraser has shown that it is likewise a cardiac poison. He poisoned a retriever dog, and while the respirations were actually increased by one in the minute, the pulsations of the heart were diminished by one half. This poison must, therefore, be considered to act on the heart directly, and not solely by its secondary effects on the respiration. Fraser concludes that the bean does not affect the heart through the vagi nerves, but through the cardiac ganglia.

Solutions of Calabar bean added to blood made the red corpuscles of rabbits and dogs irregular, but effected no changes in those of birds or frogs, nor in the white corpuscles of any animal Dr. Fraser examined.

The solutions appear to produce no change in the respiratory function of the blood.

The lymph hearts of frogs became paralysed at an early stage of the experiments.

The intestines of animals poisoned by the bean moved at first with increased vigour, but at last contracted so as considerably to lessen the calibre of the gut, which afterwards became dilated again. The movements continued some time after death, except after a large dose of poison, when the movements were slight, and soon ceased.

In rabbits poisoned by this bean Fraser noticed peristaltis in the cornua and body of the uterus, and in the ureters.

Calabar bean when swallowed, as is well known, causes the pupil to contract; but this effect is still more marked if a solution is dropped into the eye. Whether this contraction is produced through the sympathetic or otherwise is still an open question.

Dr. Robertson, who has paid great attention to the effect of Calabar bean on the eye, finds that even before the pupil begins to contract, the power of accommodation is lost, and that objects can be seen only at a limited distance of about a foot, all beyond appearing hazy and indistinct. The accommodating power, being affected before the pupil, is also the first

to recover itself. Objects at all distances appear nearer, and larger, than they really are. The bean induced in the affected eye a sensation as of much straining and heaviness, like that occurring after a close inspection of fine objects.

About twenty minutes after the application of the solution, the pupil contracted to one half, and the field of vision was still further shortened. The contraction may increase for an hour or more, the sight of the other eye meanwhile remaining natural. The contraction ultimately slowly yields, but more than twenty-four hours may pass before the pupil resumes its natural size. The contraction may be extreme, when, but little light finding its way through the narrowed pupil, the opposite pupil may dilate sympathetically.

Dr. Robertson has further shown that, in their action on the eye, belladonna and Calabar bean are directly antagonistic. The bean is freely used to produce contraction of the pupil.

Dr. Fraser has obtained some curious results from the topical application of solutions of Calabar bean to different structures of the body, He applied some solution of Calabar bean to the trunk of the sciatic, choosing this nerve on account of its comparative freedom from bloodvessels, and found to his astonishment that sensory conductivity was lost sooner than motor, and became at last completely destroyed. This loss of power to conduct sensory impression was not produced by mere imbibition of the fluid altering the physical state of the nerves, as other nerves kept moistened by water for a like time underwent no similar functional alteration. The completeness of this loss of power to conduct afferent impression was well shown by poisoning the animal by strychnia, after which no convulsive movement could be excited by irritating the structures below the poisoned sciatic nerve.

The irritability of the gastrocnemius was also destroyed by the local employment of strong solutions of the bean. This, too, was proved not to be due to mere imbibition.

When the solution was painted on parts of the intestines, these became relaxed, and the vermicular movements, on

reaching these points, skipped over them, and continued in the portions beyond.

We now come to the therapeutical application of this remedy. It was some time ago suggested that the Calabar bean might prove of much service in tetanus and chorea, and Dr. Fraser has lately written an interesting paper on this subject, from which we again largely borrow. Finding that the effects of strychnia on the frog can be arrested, he believes that the bean may be used with the greatest benefit in tetanus. Dr. Fraser very naturally insists on the importance of employing the drug at the very beginning of the attack, and enforces the value of this advice by the remark, that it has now been shown that when muscles contract they beget a substance which excites muscular contraction; and, further, that at the beginning of tetanus only a limited part of the cord or of the ganglia of the brain is affected, but, on the continuance of the attack, the whole of the structures become speedily involved. He disadvises the employment of the powder, mainly, on account of its tardy action. The extract should always be used either in the form of pill or in a solution in weak spirit of sp. gr. 0·920 (thirty-two grains to the fluid ounce). Dr. Fraser says that "Physostigma may be administered by the mouth, anus, or subcutaneously; and the special peculiarities of each case will be the best guide in determining which of these should be used. I should myself feel inclined always to commence the treatment by subcutaneous injection, to repeat such injection until the system is decidedly affected, and then to administer the remedy by the mouth, in a dose three times as large as is found necessary by subcutaneous injection.* Such a plan might be quite safely followed in a child of even nine years. If the remedial effects continue to be produced by administration by the mouth, it

* Dr. Eben Watson has not obtained good effects from hypodermic injection and prefers to administer the drug by the mouth or rectum. He insists on the necessity of giving enough of the extract to produce relaxation of the spasms. He has given it to the extent of seventy-two grains in twenty-four hours.

should be persevered with; for such administration has obvious advantages as far as the convenience of the practitioner is concerned. In the more severe cases, however, I believe subcutaneous injection should be alone employed. The distress and increase of spasm caused by swallowing, or the impossibility of introducing substances by the mouth, will render this necessary. I cannot, also, urge too strongly that subcutaneous injection should always be used when severe and continuous spasms occur, when a fatal result is imminent from the exhaustion caused by prolonged and frequent convulsions, and when apnœa threatens at once to close the tragic scene. By it we obtain the quickest and most powerful effects. Administration by the anus will be rarely necessary. It may, however, be employed to relieve the stomach, and will then be occasionally useful.

"From the preceding remarks it cannot be expected that any arbitary rules of dosage can be laid down. For an adult, one grain of the extract by stomach, or one-third of a grain by subcutaneous injection, will be generally sufficient to commence with. This should be repeated in two hours, when its effects will usually have passed off, and the succeeding doses may be modified according to the experience that will thus be gained. When used by subcutaneous injection, the dose of extract should be carefully mixed with ten or fifteen minims of water. This mixture has always an acid reaction, which is sometimes so decided as to produce slight irritation of the cellular tissue; but this can be avoided by carefully neutralizing the mixture with a solution of carbonate of soda. Suppositories, made with oil of theobroma and white wax may be employed when administration by the anus is desired. Each of these should contain two grains of extract. For children we must be guided by the general rule of employing, according to age, one-third or one-fourth, or even less, of the above doses. It will be found necessary to repeat these doses frequently—every hour, every hour and a half, or every two or three hours—and, of course, the severity of the disease and the effect of the remedy will be the best indication

for this. The great object is to produce as quickly as possible, and then to maintain, the physiological effect of physostigma in diminishing reflex excitability. The doses must, therefore, be continued in increasing quantities until this physiological effect is produced, or until the sedative action of the drug on the circulation is carried to a dangerous extreme, or until constant nausea and vomiting compel us to desist.

"This nausea is, I believe, due to the action of physostigma in causing energetic contractions of the stomach and intestines. To this cause may also be referred a peculiar epigastric sensation, which is one of the first symptoms of the action of this drug, whether it be administered by the stomach or subcutaneously, and which is always relieved by eructation. The catharsis that physostigma causes—probably an advantageous effect in tetanus—is another result of this intestinal contraction, though it is also due to an increase of secretion by the intestinal glands.

"Another physiological effect of physostigma is excessive perspiration. This is most strikingly observed when a large dose is administered by subcutaneous injection. It may be of some importance in the treatment of tetanus, for sudorifics are vaunted as reliable remedies for this disease; but as I am at a loss to understand why perspiration should in itself prove beneficial, I mention it only as an indication that physostigma is affecting the system.

"It might reasonably be expected that the active principle of physostigma—eseria—should be valuable in tetanus, and especially for administration by subcutaneous injection. It is, however, an alkaloid that is very difficult to prepare, and as far as my knowledge of its properties is concerned, it appears to be somewhat unstable. There is, besides, but little advantage in employing a more active remedy than the extract of physostigma.

"In these observations, no distinction has been drawn between the traumatic and idiopathic varieties of tetanus. As far as treatment is concerned, they only differ in this, that the traumatic variety is usually the more severe and acute, and

that it therefore generally demands a very energetic and active employment of the remedy."

Dr. Fraser next makes a few remarks on the influence of this remedy over chorea, but at present there appears to be little evidence on this subject. "The treatment of this disease," he says, "will rarely require to be so active or energetic as that recommended for tetanus. Physostigma should be administered either in the form of powder or of tincture. From three to six grains of powder, three or four times daily, may be given to children, and from ten to twenty grains, as frequently to adults."

Dr. Crichton Browne finds Calabar bean markedly useful in general paralysis of the insane; indeed, he has discharged some of his patients cured of this severe disease. I have known it arrest the progress of this disease, and even slightly improve the mental and physical condition. I have seen it not only arrest progressive muscular wasting, uncomplicated with much mental disorder, but also effect considerable improvement in the muscular power. Moreover, it has appeared to me to effect some good in cases of long standing hemiplegia. I have given the extract of physostigma in one-thirtieth of a grain doses every two hours.

THERAPEUTICS OF BELLADONNA.

Certain animals, like pigeons and rabbits, appear to be almost insusceptible to the influence of belladonna. Dr. Horatio Wood has shown that, locally applied, belladonna does not dilate the pupil of pigeons, which confirms Wharton Jones's observation that neither does it when administered internally. Not only belladonna, but also stramonium and hyoscyamus, have very little action on pigeons, it being almost impossible to kill them with these substances. Two grains of atropia administered hypodermically, are required to kill a pigeon,